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MAINE'S CENTER FOR FUNCTIONAL MEDICINE AND THE HEALING ARTS

## **Correlation of High-Sensitivity C-Reactive Protein marker of Inflammation and Metabolic Screening Questionnaire**

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### **Abstract**

**BACKGROUND:** Inflammation has been shown to be a strong contributing factor to several chronic diseases, such as coronary artery disease, type 2 diabetes, and hypertension. Functional Medicine ([www.functionalmedicine.org](http://www.functionalmedicine.org)) is a biomedically based, nutritionally oriented medical approach rooted in the idea that many disease states are secondary to inflammation. One tool used in Functional Medicine to assess levels of inflammation is the Metabolic Screening Questionnaire (MSQ). The MSQ was derived from the Cornell Medical Index, using those questions describing symptoms thought to be related to inflammation. This study evaluates the Metabolic Screening Questionnaire (MSQ) as a valid and useful tool to detect and follow inflammation by correlating MSQ scores with high-sensitivity C-reactive protein (hsCRP) blood levels.

**HYPOTHESIS:** High MSQ scores will statistically correlate with elevated hsCRP levels.

**METHODS:** 140 charts were reviewed for MSQ and hsCRP data from the years 2004-2007. The questionnaires were filled out at annual exams and hsCRP levels drawn periodically to monitor for inflammation. The MSQ asks about the frequency and severity of specific symptoms within the 4 weeks prior to filling out the questionnaire. 59 questionnaires and hsCRP levels taken within 21 days of each other were collected and used as data points. The 59 patients were all female, ages 33-74.

**RESULTS:** A Pearson correlation was used to analyze the data pairs, and a small but statistically non-significant correlation was found ( $r=.210$ ,  $p=.111$ ).

**CONCLUSION:** This study's results show that the MSQ does not specifically measure inflammation as correlated with hsCRP levels. However, further studies with a larger sample size are needed to confirm this conclusion. Functional Medicine is at the forefront of medical approaches using biomedical, genetic individuality, nutrition, and patient-centered care. It is beneficial for practitioners to be aware of the possible limitation of the MSQ in evaluating patients' inflammatory risk and progress over time.

### **Introduction**

Inflammation has been shown to be a strong contributing factor to several chronic diseases, such as coronary artery disease (CAD), hypertension, type 2 diabetes, and obesity.<sup>10 13 17 18</sup>

Functional Medicine is a biomedically based, nutritionally oriented medical approach rooted in the idea that many disease states are secondary to inflammation and toxicity. The Institute of Functional Medicine ([www.functionalmedicine.org](http://www.functionalmedicine.org)) was founded in 1991 by Jeffrey Bland, PhD, a nutritional biochemist who has worked at the Linus Pauling Institute. He developed the concept of biomedical individuality, each of us having a unique combination of molecular genetics and thus cell physiology.

Common chronic disorders treated by Functional Medicine practitioners include Alzheimer's disease and other dementias, asthma, coronary artery disease and atherosclerosis, chronic

fatigue, depression, insulin resistance and diabetes, irritable bowel syndrome and inflammatory bowel disease, menopause, rheumatoid arthritis, and allergies.<sup>12</sup>

Functional Medicine practitioners use nutritional anti-inflammatory foods to modulate inflammatory pathways. For example, for CAD risk, walnuts, rich in polyunsaturated fatty acids and linoleic acids, have been shown to lower cholesterol and influence endothelial function, inhibiting platelet aggregation, monocyte adherence, chemotaxis, and vascular smooth muscle cell proliferation.<sup>6</sup> In addition, omega-3 fatty acids in fish oil have been shown to have anti-inflammatory effects.<sup>8 11</sup>

The Institute of Medicine (IOM) report on the future of quality in medicine, "Crossing the Quality Chasm" identifies 10 New Rules (Appendix A) to replace the current approach in medicine.<sup>4</sup> Functional Medicine is congruent with many of these new rules. For example, gene polymorphisms are used to determine individual physiological functioning, resulting in customized care for each patient. Safety is prioritized with emphasis on dietary changes and nutritional supplements over pharmacological treatment. The focus of Functional Medicine is upstream, preventative and evidence-based.

At least 30,000 clinicians have been trained to use the Metabolic Screening Questionnaire (MSQ) (Appendix B) as part of their evaluation of a patient's health.<sup>12</sup> The MSQ is a tool derived from the Cornell Medical Index, and is used by Functional Medicine practitioners to assess symptoms that are related to inflammation. It has been found to correlate fairly highly with the Dynamic SF-36 Health Quality of Life Survey (Pearson correlation  $r = (-) 0.635$ ).<sup>19</sup> It is in some ways similar to allopathic medicine's Review of Systems, however, it is less extensive, and specifically designed to pick up symptoms that are markers of inflammation. The MSQ tool has been used in detoxification programs to evaluate improvement in health, using it as a marker of toxicity and inflammation.<sup>3</sup>

Our question in this study is whether indeed the MSQ correlates with inflammation. If so, it can continue to be used as a marker of inflammation as well as a patient's symptoms. If not, perhaps the MSQ is not the most valid tool to be using.

This research was conducted at True North Health Center in Falmouth, Maine, an integrative medicine center which houses several physicians and practitioners who use a Functional Medicine approach. They have adapted their practices to using the MSQ with patients at annual visits. The MSQ functions in multiple ways – for example, it is useful to compare to prior questionnaires to see any improvement or worsening of symptoms, and also can bring a new symptom to the clinician's attention, adding to the patient's history.

High-sensitivity C-reactive protein (hsCRP) is a nonspecific marker of inflammation and in this study was correlated to scores on the MSQ.

CRP was discovered in 1930 by Tillet and Francis, who were researching acute pneumonia. CRP formed as a precipitate within the acute phase serum reaction with the pneumococcal cell wall C-polysaccharide, and continues to be associated with the acute-phase response to infection.<sup>9</sup>

Although CRP is known to be an acute phase reactant in first-line innate host defense during acute bacterial illness,<sup>20</sup> CRP has also been shown to be a marker of cardiovascular disease<sup>2 5 18</sup>, as well as insulin resistance and type 2 diabetes.<sup>17</sup> In addition, hsCRP is elevated with cigarette smoking<sup>13</sup>, hypertension<sup>13</sup>, and Body Mass Index (BMI)<sup>10</sup>.

Chronic inflammatory processes such as rheumatoid arthritis<sup>16</sup> and chronic lung disease<sup>14</sup> lead to an elevated hsCRP as well. In addition, the CRP gene has polymorphisms which influence the blood level of each individual.<sup>9</sup> Clearly, hsCRP is nonspecific, but is potentially an important clinical marker, and appropriate to use for the investigation of this study.

## Methods

This was a retrospective study. One hundred and forty charts (140) charts were reviewed for MSQ score and hsCRP value data from the years 2004-2007.

MSQ questionnaires were filled out by patients at annual physical exam visits.

High-sensitivity CRP levels were ordered to assess inflammation, and were drawn from multiple laboratories in Maine (Affiliated Laboratories, Geneva Laboratory/Greater Smokies, NorDex, Maine General Hospital Lab) with normal values ranging from 0 – 3.0 mg/L. (The American Heart Association and CDC have defined risk groups for heart disease as: low risk less than 1.0 mg/L, average risk 1.0-3.0 mg/L, and high risk above 3.0mg/L.)

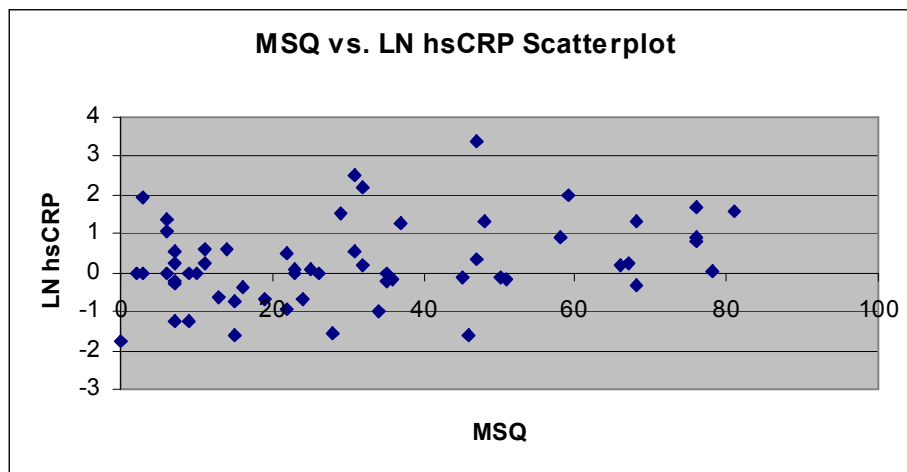
Dates of each value were recorded, and the time interval between MSQ completion and hsCRP lab collection were calculated. Of the 140 charts reviewed, 59 had an interval of 0-21 days between MSQ and hsCRP data, with the remaining charts having data with an interval greater than 21 days. 21 days was chosen given that the MSQ data is reported based on symptoms over a 4 week period.

The 59 resulting data sets were chosen for statistical analysis using a Pearson correlation. All patients were female, ages 33-74.

## Results

Pearson correlation  
( $r=.210$ ,  $p=.111$ )

The hsCRP values did not assume a normal bivariate distribution, and thus the data correlation was graphed using a natural log transformation using Microsoft Excel.



**Figure 1: Scatterplot of MSQ scores vs. natural log of hsCRP values**

(See Appendix C for raw data)

## Discussion/Conclusion

There is a slight correlation of  $r = 0.210$ , visualized in figure 1 as a slight upward angle to the data points, showing that higher Metabolic Screening Questionnaire scores may be linked to higher hsCRP blood levels. This is however statistically insignificant, and limited by the small power of this study. With the current sample size, there is only about 50% power. With the help of epidemiologist Lee Lucas, PhD, from Maine Medical Center's Center for Outcomes Research and Evaluation (CORE), we determined that to reach 80% power with a

p value of 0.05 and show that the true correlation in the population is 0.210, an  $n$  of at least 153 would be needed. Moreover, 0.210 is not a very strong correlation.

This study is also limited by its retrospective nature. In a prospective study, a larger cohort could be studied, with both MSQ results and hsCRP levels followed over time as opposed to this study's reference of one point in time for each participant. This would be very important, to assess for chronically elevated hsCRP levels or MSQ scores, and would lessen the possibility of an acute illness raising the hsCRP at one point in time. Moreover, in a prospective study, the hsCRP could be drawn on the same day the MSQ is filled out, to lessen the date discrepancy confounding variable. Another limitation of this study is that all participants are women ages 33-74, so results do not apply to men or other age ranges. There may be a selection bias, in that women who choose to see a Functional Medicine specialist might have higher levels of inflammation than the population at large.

Many of the symptoms on the questionnaire could be secondary to health problems such as the common cold, or are nonspecific, such as hearing loss or constipation, which could be from multiple etiologies, such as infectious, dietary, or anatomic variants. In addition, the questionnaire's scale of 1-4 asks about both frequency and quality of symptoms without differentiation.

This study indicates that the MSQ may not be a valid way to track inflammation. The practical role of MSQ could be to alert the practitioner of symptoms to assess further, and allow them to be followed over time with treatments, dietary and lifestyle changes. An acute increase of MSQ score or a chronic elevated score would inform the practitioner of an imbalance to be investigated.

It is clear that there is an association between inflammation and chronic diseases such as type 2 diabetes and coronary artery disease. Chronically elevated hsCRP levels are associated with higher mortality. Persistently elevated hsCRP values ( $> 3$  mg/L) are indicators of an ongoing disease process such as coronary heart disease, cerebral vascular disease, and cancer.<sup>13</sup> Although hsCRP is a general indicator of inflammation, it is clear that it may be helpful in following disease risk, especially cardiovascular risk. In these times of increasing obesity in this country, it is also interesting to see that the association between obesity and cardiovascular disease may be due to an increase in systemic inflammation associated with increased weight.<sup>7</sup>

On the other hand, presence of both common and uncommon inflammatory conditions can lead to elevated hsCRP levels, causing a need for caution when associating hsCRP with cardiovascular risk.<sup>5</sup> Full assessment of contributing factors and awareness of all conditions is essential when using a nonspecific marker such as hsCRP.

It could be helpful to repeat this study with biomarkers other than hsCRP which have been used to track inflammation, including Interleukin-6 (IL-6), tumor necrosis factor alpha (TNF alpha), and soluble receptors for TNF (sTNFR1 and sTNFR2).<sup>14</sup>

The increasing awareness of the role of inflammation in chronic disease indicates a greater need for the science and perspective of Functional Medicine.

In summary, this study's results show that the MSQ does not specifically measure inflammation as correlated with hsCRP levels. However, based on the small sample size and confounding variables mentioned above, further studies are needed to confirm this conclusion. Neither the hsCRP test nor the MSQ questionnaire can be used as an absolute diagnostic method for inflammatory or chronic diseases, but both may be helpful tools to monitor and evaluate inflammatory risk and progress over time.

## Resources

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**Appendix A: 10 New Rules (“Crossing the Quality Chasm” Institute of Medicine Committee on the Quality of Healthcare in America)**

1. Continuous Healing Relationships instead of Care based on visits
2. Customized Care for Patients instead of Professional autonomy
3. Patient is source of control instead of Professionals control care
4. Information flows freely instead of Information is a record
5. Decision making is evidence-based instead of Decision making based on training& experience
6. Safety is a system property instead of Safety is individual responsibility
7. Transparency is necessary instead of Secrecy is necessary
8. Needs are anticipated instead of The system reacts to needs
9. Waste is continuously decreased instead of Cost reduction is sought
10. Cooperation is a priority instead of Professional roles trump the system

## Appendix B. Metabolic Screening Questionnaire (MSQ)

Rate each of the following symptoms based upon your typical health profile for the past 30 days

### Point Scale

- 0 - *Never or almost never* have the symptom
- 1 - *Occasionally* have it, effect is *not severe*
- 2 - *Occasionally* have it, effect is *severe*
- 3 - *Frequently* have it, effect is *not severe*
- 4 - *Frequently* have it, effect is *severe*

### HEAD

- \_\_\_\_\_ Headaches
  - \_\_\_\_\_ Faintness
  - \_\_\_\_\_ Dizziness
  - \_\_\_\_\_ Insomnia
- Total \_\_\_\_\_

### EYES

- \_\_\_\_\_ Watery or itchy eyes
  - \_\_\_\_\_ Swollen, reddened or sticky eyelids
  - \_\_\_\_\_ Bags or dark circles under eyes
  - \_\_\_\_\_ Blurred vision
- Total \_\_\_\_\_

### EARS

- \_\_\_\_\_ Itchy ears
  - \_\_\_\_\_ Earaches, ear infections
  - \_\_\_\_\_ Drainage from ear X
  - \_\_\_\_\_ Ringing in ears, hearing loss
- Total \_\_\_\_\_

### NOSE

- \_\_\_\_\_ Stuffy nose
  - \_\_\_\_\_ Sinus problems
  - \_\_\_\_\_ Hay fever
  - \_\_\_\_\_ Sneezing attacks
  - \_\_\_\_\_ Excessive mucus formation
- Total \_\_\_\_\_

### MOUTH/THROAT

- \_\_\_\_\_ Chronic coughing
  - \_\_\_\_\_ Gagging, frequent need to clear throat
  - \_\_\_\_\_ Sore throat, hoarseness, loss of voice
  - \_\_\_\_\_ Swollen or discolored tongue, gums, lips
  - \_\_\_\_\_ Canker sores
- Total \_\_\_\_\_

### SKIN

- \_\_\_\_\_ Acne
  - \_\_\_\_\_ Hives, rashes, dry skin
  - \_\_\_\_\_ Hair loss
  - \_\_\_\_\_ Flushing, hot flashes
  - \_\_\_\_\_ Excessive sweating
- Total \_\_\_\_\_

### HEART

- \_\_\_\_\_ Irregular or skipped heartbeat
  - \_\_\_\_\_ Rapid or pounding heartbeat
  - \_\_\_\_\_ Chest pain
- Total \_\_\_\_\_

### LUNGS

- \_\_\_\_\_ Chest congestion
  - \_\_\_\_\_ Asthma, bronchitis
  - \_\_\_\_\_ Shortness of breath
  - \_\_\_\_\_ Difficulty breathing
- Total \_\_\_\_\_

### DIGESTIVE TRACT

- \_\_\_\_\_ Nausea, vomiting
- \_\_\_\_\_ Diarrhea

	_____	Constipation	
	_____	Bloated feeling	
	_____	Belching, passing EXCESSIVE gas	
	_____	Heartburn	
	_____	Intestinal/stomach pain	Total _____
<b>JOINTS/MUSCLE</b>	_____	Pain or aches in joints	
	_____	Arthritis	
	_____	Stiffness or limitation of movement	
	_____	Pain or aches in muscles	
	_____	Feeling of weakness or tiredness	Total _____
<b>WEIGHT</b>	_____	Binge eating/drinking	
	_____	Craving certain foods	
	_____	Excessive weight	
	_____	Compulsive eating	
	_____	Water retention	
	_____	Underweight	Total _____
<b>ENERGY/ACTIVITY</b>	_____	Fatigue, sluggishness	
	_____	Apathy, lethargy	
	_____	Hyperactivity	
	_____	Restlessness	Total _____
<b>MIND</b>	_____	Poor memory	
	_____	Confusion, poor comprehension	
	_____	Poor concentration	
	_____	Poor physical coordination	
	_____	Difficulty in making decisions	
	_____	Stuttering or stammering	
	_____	Slurred speech	
	_____	Learning disabilities	Total _____
<b>EMOTIONS</b>	_____	Mood swings	
	_____	Anxiety, fear, nervousness	
	_____	Anger, irritability, aggressiveness	
	_____	Depression	Total _____
<b>OTHER</b>	_____	Frequent illness	
	_____	Frequent or urgent urination	
	_____	Genital itch or discharge	
			Total _____
<b>GRAND TOTAL</b>			<b>TOTAL</b> _____

**Appendix C: Raw data: Pairs of MSQ scores-hsCRP (mg/L) values for 59 subjects.**

<b>MSQ</b>	<b>hsCRP</b>	<b>MSQ</b>	<b>hsCRP</b>
7	1.72	13	0.53
25	1.09	7	1.3
14	1.81	9	0.28
3	0	47	30.2
2	0	68	0.71
81	4.9	48	3.74
23	0	11	1.79
32	1.2	58	2.53
26	0	7	0.82
6	2.94	22	1.61
24	0.5	35	0.81
78	1.05	28	0.21
19	0.5	46	0.2
31	12.4	76	2.27
76	2.55	45	0.9
10	0	15	0.49
11	1.3	67	1.3
31	1.7	23	1.11
76	5.39	7	0.78
37	3.64	22	0.39
32	9.02	66	1.18
6	0	7	0.29
9	0	15	0.2
0	0.17	59	7.44
35	0	34	0.37
3	6.9	68	3.8
36	0.85	51	0.84
16	0.7	47	1.4
50	0.9	29	4.66
		6	4.03